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Cystic Fibrosis

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NATIONAL INSTITUTES OF HEALTH

National Institute of Arthritis, Diabetes,
and Digestive and Kidney Diseases

CYSTIC FIBROSIS

Cystic fibrosis (CF) is the most common lethal inherited disease in Caucasians. An estimated 1 in 20 Caucasians carry the gene for CF and can transmit it to their children. The disease occurs only when both parents pass on the gene. If both parents carry the gene but do not have the disease, each of their children has a 1 in 4 chance of having CF. Approximately 1 in 2,000 newborns have CF, and these children have a 50-50 chance of living to the age of 21.

CF has three characteristic signs: lung and digestive problems, and elevated amounts of salt in sweat. Of these, lung disease is the most deadly aspect of this disorder. The mucus in the lungs of CF patients is thicker and more copious than normal. Breathing can be difficult and recurrent bacterial infections cause progressive lung damage.

The same thickening of mucus occurs in all the organs that produce external secretions. These organs, called exocrine glands, include the sweat glands in the skin, a part of the pancreas that produces digestive enzymes, and mucus-secreting glands in the lungs. The pancreas produces enzymes that are important for digesting fats. In someone with CF, pancreatic secretions are viscous and the release of important enzymes to the digestive tract is impaired. The result is abdominal pain, foul-smelling stools, and malnutrition.

Treatment of CF is aimed at lessening these lung and digestive problems. The three characteristic conditions--lung and digestive disease and high salt content in sweat--are, in addition to being clues to diagnosis, the keys to discovering how the inheritance of two genes results in such grave illness. Scientists are studying the problem of CF from several directions in order to find the first step in the chain between the CF gene and the illness it causes. This first step may be the production of an unusual protein or a defect in a critical enzyme. The answer will tie together the very different effects this disease has.

The CF Puzzle

A combination of different therapies to treat the lung and digestive effects of CF are now the mainstay of treatment for the disease. Enzyme supplements are used to treat pancreatic deficiency, while for the lung disease, treatment includes special physical therapy to loosen and help eliminate mucus from the lungs, antibiotics to combat the lung infections, and the use of

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oxygen. The current life expectancy of 21 years for a person with CF represents an improvement over previous years due to advances in treatments such as these. Research is also under way to further increase the effectiveness of the therapy, for example, in the area of antibiotic effectiveness. This research is important because it is these secondary effects of CF that make the disease so deadly. However, it is possible that much greater improvements in life expectancy may require understanding and treatment of the disease at a more fundamental level.

CF is associated with a variety of effects that have proved difficult to link together. The lungs of people with CF, for example, seem to lack immunity to infection. The composition of a variety of body secretions and certain nervous system responses seem to be different in people with CF than in people without the disease. CF patients also develop symptoms of the disease to different extents. Carriers of the CF gene do not develop CF, but they do respond to certain physical tests in a manner similar to people with the disease.

One approach to CF research has been to characterize thoroughly each of these abnormalities and to determine if any represent a fundamental or primary defect that could explain all the others.

Sweat and Electrolytes

The lung and digestive effects of CF can be mistaken for other conditions in an infant. There have been cases reported in which the disease has not been correctly diagnosed for years. A test developed by Dr. Paul di Sant'Agnese, scientist emeritus in the intramural NIADDK program, is now used to confirm the diagnosis. The test measures the salt content of sweat. The results are always higher in CF patients than in people without CF.

Because elevated salt content is present in 100 percent of these patients, researchers have used it as a key to exploring the basic CF defect. A major advance in recent years was the identification by Dr. Paul Quinton at the University of California at Riverside of what appears to be the reason that salt or sodium chloride content remains high in sweat. Dr. Quinton found that chloride is not able to move as freely across cell membranes in the sweat glands of CF patients as in people without CF. This research has been confirmed in studies of respiratory tissues, and investigators are now looking at salt balance in pancreatic cells.

The production of sweat depends to some extent on neurological control. Dr. Kenzo Sato at the University of Iowa in Iowa City has found that the response of sweat glands to neurochemical stimulation in CF patients is defective compared with the response in people without the disease. Dr. Sato has also narrowed down the stage in the metabolic sequence of stimulation at which this defective responsiveness could occur. While differences in the reabsorption of salts takes place in one part of the sweat gland,

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this difference in responsiveness occurs in another part of the sweat gland that secretes fluid before reabsorption takes place. Variations in the control of this process may help explain neurologic differences observed elsewhere in the body.

Neurologic Stimulation and the Lungs

Differences in responsiveness to certain kinds of neurochemical stimulation have shown up in other ways in people with CF. Dr. Pamela Davis, working at the NIADDK-supported CF center at Case Western Reserve University in Cleveland, found that people who were known to be carriers of the gene for CF (because they had children with the disease) showed a variety of differences in neurologic responsiveness, similar to those seen in their children. Of particular interest was the finding that altered neurologic response manifests itself in the lungs of many of the parents of children with CF in a manner similar to that seen in their children. Similar differences in neurologic response have been correlated in the past with increased airway sensitivity to irritants or stress in people with asthma. If a difference in neurologic responsiveness can be identified in more than one system in the body, and if it can explain some of the different CF symptoms, it may be another candidate for a basic CF defect.

Pancreatic Secretion

Scientists are looking for parallels in the problems of exocrine secretion in the pancreas and other exocrine organs like the lungs and sweat glands. Dr. Stephen Ernst at the University of Michigan in Ann Arbor has been looking at electrolyte (salt) metabolism in secretory cells of the pancreas. He reports that compounds that promote secretion also increase the exchange of sodium and potassium across cell membranes. Further research will clarify the relationship between this finding and the nature of salt exchange in this organ.

Genetics

CF is clearly a genetic disease. Much can be learned from studying the patterns of inheritance of CF. For example, CF occurs with equal frequency in boys and girls, indicating that the gene is not present on one of the human genes that determines sex.

Family pedigrees can sometimes reveal which chromosome carries an abnormal gene. With currently available techniques in molecular genetics, it is now possible to actually identify the alteration in genetic molecular material that constitutes the genetic abnormality. Because scientists understand more and more about how genes are translated into proteins, this information could lead to identification of the underlying abnormal compound or metabolic process that causes CF.

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Laying the groundwork for studies of this nature is research on families with CF. Dr. Katherine Klinger at Case Western Reserve University's CF center in Cleveland has been studying two Amish communities in Ohio. The Amish are a religious group, the members of which marry within the community. As a result, many Amish share ancestry with others in their communities. In one of the Amish communities, the incidence of CF is 1 in 569, much higher than the 1 in 2,000 rate in the rest of the United States. In the other Amish community, CF has not been reported. Dr. Klinger has traced the families in the community with CF to a single ancestral couple. Such studies provide important information for future research to determine why the lethal CF gene is so frequent in some populations and to provide the means to identify alterations in genetic material that correspond with the disease.

Immunology

The lungs of people with CF are particularly prone to bacterial infections, implying that their immune response to these infections is abnormal. An important line of research is the study of the immune system of CF patients to see how their immunological response is different from that of people without CF. Dr. Michael Parmely at the University of Kansas Medical Center in Kansas City has identified more than one bacterial product from Pseudomonas aeruginosa, the most common bacteria that affects individuals with CF. These bacterial products stimulate immune response in individuals without CF. He suggests that the abnormal immune response in CF patients to infection probably involves several bacterial products or antigens.

In other immunological research, Drs. Rita Margolies and Thomas Boat at Case Western Reserve University have found that in people with CF the carbohydrate content in one type of disease fighting or antibody molecule, IgG or gamma globulin, is altered. They suggest that such an alteration may help explain differences noted in the presence and activity of IgG when comparing people with CF with people without the disease.

NIADDK Intramural Program

The NIADDK intramural program has developed a major new initiative in CF during the past year. A CF research program has taken shape with the arrival of five research fellows who will conduct studies under the guidance of expert NIADDK preceptors in a variety of areas related to CF. They will look at the fundamental mechanisms involved in CF. Work is under way in the areas of ion transport, mucus and exocrine secretory problems, infections and immunology, genetics, and the structure and metabolism of glycoproteins, compounds that are important in the structure of mucus and immune substances. These fellowships are supported in part by funds from the Cystic Fibrosis Foundation. It is hoped that the interdisciplinary work that this new program makes possible will contribute to the training of expert medical researchers in areas of research that are fundamental to an understanding of the basic defect(s) associated with CF.

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The major abnormality in CF is thickened mucus. Serous glands in the airways' mucosa produce a thin, watery secretion and serous cells in the epithelium produce thick secretions. The secretions of these two glands combine with water to form the airway mucus that serves as a protective coating in the normal airway. In CF patients, however, the airway mucus is abnormally thick and viscous, which impedes the action of cilia in cleansing the airways of inhaled particulate matter. The most significant complication of the thick mucus produced by CF patients is the chronic lung disease resulting from infections caused by Staphylococcus aureus and Pseudomonas aeruginosa, the immediate cause of death in over 90 percent of cases.

Recent studies have suggested that patients with CF, especially those with asthma, be screened for another potentially destructive pulmonary disorder--allergic bronchopulmonary aspergillosis (ABPA), which is caused by a fungus.

National Heart, Lung, and Blood Institute (NHLBI) grantee Dr. Jordan N. Fink and other investigators at the Medical College of Wisconsin in Milwaukee, Marcus Center for Immunologic and Allergy Research at Wood Veterans Administration Medical Center in Milwaukee, the Cystic Fibrosis Clinic of Milwaukee Children's Hospital, and the Northwestern University Medical School in Chicago, reported screening 100 patients with CF for ABPA. Using skin reactivity and other immunological tests, the investigators determined that 10 percent of these patients were positive for ABPA.

The presence of aspergillosis in CF patients reduces treatment effectiveness and hastens the progress of the disease. The investigators recommend, therefore, that all CF patients be screened and appropriate early treatment for ABPA be initiated to prevent a hastened disease process.

Currently, researchers funded by NHLBI are investigating the movement of chloride and other ions across membranes. This influences the movement of water across membranes and therefore in and out of cells. Detection of abnormal or inappropriate ion movements may lead to the means to stabilize ionic migration and with it, water movement.

Other research is directed toward the detection of CF gene carriers. At present a test does not exist for this purpose, and genetic linkage techniques are being used in attempts to isolate the genetic marker in CF. The discovery of the location of the CF gene on the human chromosome would be the avenue to development of a prenatal test for CF and for the

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identification of individuals who are carriers. Such a test might be one that detects the DNA mutation that causes CF, for example, an antibody or functional test to detect the presence of the altered gene or its product.

Other NHLBI research that bears directly or indirectly on CF includes projects aimed at improving the treatment of lung infections, developing better methods to deliver therapeutic agents directly to affected areas of the lung, and identifying the relationship between nutritional status and the degree of respiratory impairment by CF.

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National Institute of Dental Research

Patients with CF develop chronic pulmonary disease and digestive problems, as well as abnormal changes in sweat and in the salivary glands that produce saliva. Saliva plays a key role in protecting the mouth against infection. Saliva also lubricates the oral tissues, and initiates food breakdown and the oral phase of swallowing.

Normally a clear, free-flowing fluid, the saliva of CF victims may be thick and sticky, dominated by mucous secretions. This thick fluid can block the salivary ducts, or pathways, causing the glands to enlarge and become vulnerable to infection. The abnormal saliva also contributes to functional problems--difficulties in speech, taste, and swallowing--and increases the risk of dental and oral soft tissue diseases.

The National Institute of Dental Research (NIDR) conducts and supports extensive study of the exocrine (externally secreting) salivary glands to learn what mechanisms normally regulate their secretion in order to determine what goes awry in disorders such as CF. A number of scientists have focused on the salivary glands as a model exocrine gland to identify the basic defect in CF. They have learned, for example, that salivary gland secretion is under broad control of the autonomic (involuntary) nervous system. Surrounding nerves release chemical mediators or messengers, called neurotransmitters, that signal the salivary glands to form and release saliva.

Institute grantee Dr. Charlotte Schneyer at the University of Alabama in Birmingham has used an animal model of CF that results from depletion of a key neurotransmitter, norepinephrine. This deficit appears to cause several specific glandular changes, including altered calcium levels.

Many NIDR-supported scientists have focused on the hypothesis that CF is a disorder of calcium-stimulated secretory events. Dr. James Putney and colleagues at the Medical College of Virginia in Richmond, for example, have demonstrated that cellular calcium, which is mobilized in response to a secretory signal, likely comes from the endoplasmic reticulum, a cellular organelle. His research shows that a product of a cell membrane phospholipid, inositol triphosphate, probably provides the key message for calcium to be released from its cellular store.

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In related studies, Dr. David Quissell of the University of Colorado in Denver is determining what specific cellular regulatory events employ the calcium mobilized during secretory signals. In particular, Dr. Quissell is examining how free calcium participates in specific modifications of cellular proteins thought to be involved in movement of water across secretory gland cell membranes.

Several investigators have attempted to clarify actual mechanisms of water and electrolyte movement in these exocrine glands. NIDR scientists Drs. Taishin Takuma and Bruce Baum have demonstrated that salivary gland cells contain two major mechanisms for handling calcium fluxes--sodium/calcium exchange and ATP-dependent calcium transport. Similarly, Dr. Ricardo Martinez of the University of Missouri at Columbia has characterized specific mechanisms for sodium, potassium, and chloride transport in salivary glands. With NIDR support, he and his colleagues have also extensively studied developmental changes in the regulation of salivary secretion. Finally, Dr. Kenneth Izutsu, a grantee at the University of Washington in Seattle, has examined intracellular gradients of several ions (sodium, potassium, calcium, and chloride) in glands obtained from control subjects and CF patients.

Other investigators have focused on mechanisms of exocrine protein secretion. Drs. Frank Dowd of Creighton University in Omaha, Nebraska, Eileen Watson of the University of Washington in Seattle, and NIDR intramural scientist Arthur Hand have joined forces in an effort to clarify the events responsible for the release of protein into the forming saliva. Their studies suggest that a relationship exists between the membranes packaging proteins for export and the cell's limiting membrane, thus indicating a basis for directional protein movement.

In other NIDR-supported research, Drs. Michael Levine and Lawrence Tabak of the State University of New York in Buffalo have conducted extensive studies characterizing (1) the structure of carbohydrate groups in important salivary glycoproteins obtained from CF patients and controls, and (2) the role of these specific carbohydrate groups in glycoprotein antibacterial function. Recently, NIDR intramural scientists Drs. Bruce Baum, Eleni Kousvelari, and Dipak Banerji have shown that in salivary glands, addition of sugars to glycoproteins is under the control of certain neurotransmitters (the beta-adrenergic ones). Both the extent and nature of the addition of sugar groups to protein can be regulated by the beta-adrenoreceptor. It is interesting that researchers working with three systems, including sweat glands, white blood cells, and salivary glands, have demonstrated alterations in beta-adrenoreceptor function in CF. Conceivably, such changes would negatively affect glycoprotein formation and/or function in CF patients.

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National Institute of Allergy and Infectious Diseases

The National Institute of Allergy and Infectious Diseases (NIAID) supports research on respiratory infections, which are a frequent cause of death in CF patients. One pathogen that is being studied in-depth is respiratory syncytial virus (RSV).

RSV causes bronchitis, bronchiolitis (an inflammation of the bronchioles, the smallest branches of the airways), pneumonia, and croup as well as less serious infections in the nose and ears. Infection occurs early in life; virtually all U.S. children have been infected by 2 years of age. Infection during the first 6 months of life can produce particularly severe disease. RSV causes more cases of pneumonia in infants than any other virus, and an appreciable number of these infants die.

Like other acute respiratory diseases, RSV infections are especially dangerous in infants with CF. The lungs of these patients are typically clogged with thick mucus that prevents optimal lung function.

Unfortunately, the problem is further compounded by three factors. First, an effective vaccine does not exist for preventing RSV infections. Second, isolation and general public health measures, although helpful, are not completely adequate to control the spread of infection since RSV survives on environmental surfaces for long periods of time. Third, immunity after infection lasts briefly, so that reinfection is common.

Despite many studies on the incidence of disease due to RSV, very little is known about the immunologic mechanisms involved in resistance to RSV infection. Studies in humans have not defined which parts of the immune system help a person recover from disease and resist reinfection.

NIAID grantees are investigating RSV and how the immune system responds to it, with the ultimate goal of preventing or more effectively treating RSV infections.

Dr. Norbert J. Roberts, Jr., of the University of Rochester in New York, has found that RSV infection decreased the ability of white blood cells to fight infection. In general, viral infections cause some white blood cells to secrete a chemical called interferon, which helps lessen the severity of disease. Dr. Roberts has shown that RSV causes white blood cells to produce very little interferon, in contrast to other respiratory viruses such as the influenza virus, which causes production of large amounts of interferon.

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Dr. Pearay L. Ogra of Children's Hospital in Buffalo, New York, is studying the relationship between RSV and another part of the immune system--the substances such as histamine that are responsible for producing allergic and asthmatic reactions. Dr. Ogra has found that increased levels of histamine are secreted by RSV-infected patients with the worst bronchial symptoms. These observations may mean that RSV infections are somehow linked with bronchial asthma.

One reason why the interaction of RSV with the immune system has remained a mystery for so long is that there was no suitable laboratory animal in which to study RSV infection. Recently, the cotton rat has been identified as a satisfactory experimental model because its immune response to RSV infection is similar in many ways to that of humans. This finding has allowed RSV research to proceed more rapidly, particularly with regard to vaccine development.

Dr. Gregory A. Prince, an NIAID intramural scientist, has been trying to determine why an experimental RSV vaccine of the mid-1960's not only failed to protect against disease, but actually caused vaccinated infants to have unexpectedly severe illness when they became infected naturally. Using the cotton rat, Dr. Prince recently compared the effects of two vaccines: one containing virus killed with a chemical (formalin) and one containing virus killed with heat. After vaccination, the rats were exposed to live RSV. Only the group that received formalin-killed virus had enhanced disease in the lungs, suggesting that the action of formalin on the RSV in the vaccine was critical.

In other studies, Dr. Prince has been examining the protective power of RSV antibodies passed from mother to infant, either through the placenta or via breast milk. Early studies in infants had suggested that maternal antibody to RSV was actually harmful to infants and played a role in serious RSV disease. Subsequent studies showed that the highest incidence of severe disease was seen in infants 2 months of age and older, while infants under 2 months of age who had the highest levels of maternal antibody had a lower incidence of serious disease, indicating that maternal antibody was protective.

To confirm the latter studies, Dr. Prince took antibodies from cotton rats. He demonstrated that RSV antibodies have a striking effect on lung infection. The higher the level of RSV antibody in the infant rats, the less the virus was able to multiply in the lung. These results suggest that a high level of maternal antibody should provide protection against serious RSV disease during early infancy.

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Dr. Prince also tested the protective ability of human RSV antibodies in cotton rats. Animals that received human RSV antibodies prior to exposure to live RSV were completely resistant to lung infection. Further experiments in cotton rats and owl monkeys showed that human RSV antibodies may even be appropriate for treating established infections. Based on these results, clinical trials of human RSV antibodies in human infants hospitalized with RSV infections have been initiated in Washington, D.C., at the National Children's Medical Center and the Walter Reed Army Medical Center.

At the University of North Carolina at Chapel Hill, Dr. Gail T. Wertz is taking a recombinant DNA approach to RSV vaccine development. In collaboration with Dr. Laurence A. Ball of the University of Wisconsin at Madison, she recently cloned (i.e., isolated and made copies of) the 10 genes of RSV and identified which genes are responsible for directing the production of various viral proteins. The next step will be to place the appropriate genes in microorganisms, such as harmless bacteria, that will then produce large quantities of the desired proteins. These bacteria can then be used to make an experimental vaccine that will be tested in cotton rats.

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National Institute of General Medical Sciences

The National Institute of General Medical Sciences (NIGMS) funds research and research training in basic fields that provide the foundation for a better understanding of fundamental life processes. One of NIGMS' major programs supports basic research on genetics. This research supplies new knowledge, theories, and concepts that may lead to improved diagnostic techniques and treatments for many diseases, including CF.

While the hereditary pattern for transmission of CF is well-known, a genetic defect has not yet been found that can account for the disease's symptoms. Studies to identify such a defect are facilitated by the NIGMS-supported Human Genetic Mutant Cell Repository at the Institute for Medical Research in Camden, New Jersey. In 1983 the repository maintained 54 lines of cells obtained from CF patients and members of their families. This year an additional 41 lymphoblast (immature white blood cell) lines from six different families, including parents of affected children and some unaffected siblings, have been added. Cells from these lines, along with detailed background information, are made available to requesting investigators at modest charge. This enables scientists to study cells from genetically informative CF pedigrees in their own research settings without first having to locate cell donors and establish their cells in culture.

The recent success in using variations in DNA called restriction fragment length polymorphisms (RFLP's) to find a marker closely associated with the gene causing another serious genetic disorder, Huntington's disease, has stirred hope that this technique may also help researchers locate the CF gene.

NIGMS has supported much of the research to develop the RFLP technique. Dr. Raymond White of the University of Utah in Salt Lake City is among the NIGMS grantees conducting these studies, which use one of the basic tools of recombinant DNA technology, the restriction enzyme, to cut DNA at particular "recognition sites." Each restriction enzyme produces a characteristic pattern of DNA fragments, which can vary due to inherited changes in the DNA. When such changes follow the same inheritance pattern in a family as does a genetic disease, they may constitute a marker identifying a section of DNA closely linked to the gene responsible for the disease. Once such a marker is found, researchers can begin work to isolate the gene itself.

If the CF gene can be isolated, it is possible that scientists could discover the protein product for which the gene codes and that a test could be devised for the disorder. Knowledge of the gene product would also aid researchers in developing a treatment for CF.

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Division of Research Resources

CF is being studied at 17 General Clinical Research Centers (GCRC's). The Division of Research Resources (DRR) supports 75 GCRC's in major U.S. medical centers. Each year, scientists conduct more than 3,000 research studies in GCRC's, with more than 80 percent of the extramural inpatient research funded by the National Institutes of Health taking place in these centers. In addition, extensive outpatient research is also carried on.

Scientists supported by DRR's Biomedical Research Support (BRS) program also are studying CF. The program supports more than 9,000 pilot and regular health-related projects at 546 institutions in the U.S., providing a pool of flexible funds to institutions heavily involved in Public Health Service (PHS)-funded research to meet particular needs not normally covered by other grants. The funds may also complement or supplement PHS research grants by providing institutions with short-term, emergency, low-cost, interim, and shared resources.

In drug trials at the Temple University GCRC in Philadelphia, Dr. Nancy N. Huang and associates found that azlocillin, a new antibiotic, was more effective than the established antibiotic drug, carbenicillin, in treating CF patients with secondary pulmonary infections such as chronic bacterial pneumonia. CF patients are especially vulnerable to these infections because gland abnormalities result in excessive secretion of mucus, which obstructs the respiratory tract. Moreover, pulmonary infections often lead to chronic obstructive pulmonary disease, a potentially fatal complication of CF. As gauged by indicators of pulmonary function and by radiological studies, the conditions of 11 of 12 patients treated with azlocillin improved at least 20 percent. Among a second group of 14 patients treated with carbenicillin, the conditions of 9 improved at least 20 percent. The Temple University researchers found that strains of the infectious bacteria were more sensitive to azlocillin than to carbenicillin. Dr. Huang points out that further studies are needed to determine optimal dosages of azlocillin for CF patients.

Fibrosis of the pancreas and resultant malabsorption of important nutrients are common among CF patients, necessitating enzyme replacement therapy. However, in a significant minority of CF patients--perhaps as many as 20 percent--the pancreas continues to function adequately. Because a practical method to assess pancreatic function was not available, many of these

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patients undergo enzyme replacement therapy, which can cause complications. In work partially supported by the GCRC program, Dr. Baiba K. Gillard and her colleagues at the University of California at Los Angeles and the University of California at Davis developed a simple test for assessing pancreatic function in CF patients older than 1½ years of age. By measuring levels of the pancreatic enzyme isoamylase in serum samples taken from CF patients, physicians now can evaluate pancreatic function and determine whether enzyme replacement therapy is needed.

Studying another aspect of the disease, scientists at the Children's Hospital Medical Center of Northern California in Oakland and at the University of California in Berkeley examined how CF patients respond to the low tissue oxygen levels (hypoxia) characteristic of the disease. In studies supported by the BRS program, Dr. Elliot P. Vichinsky and his colleagues determined that CF patients lack the benefit of compensatory red blood cell production, an adaptation found in patients with other diseases characterized by hypoxia. The researchers also found that many of their CF patients suffered from an anemia that was due largely to a defect in red blood cell production and partly to iron deficiency. In addition, the incidence of anemia and iron deficiency increased with patient age. The scientists are continuing to investigate the biological factors responsible for these complications. They recommend that all CF patients be screened for iron deficiency and treated with iron supplements if necessary.

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Outlook

Along with the areas of research described in this report, work is under way in a number of other areas that may contribute to a final identification of the mechanism of CF. These include study of glycoproteins, which have been observed to be altered in people with CF; research on cellular proteins in CF in a search for possible altered products of a defective gene; and a search for a CF factor. Researchers have postulated that the fluids of people with CF may contain a factor, possibly an altered protein, that is perhaps a product of the CF gene and that if isolated, could be shown to cause CF-like disease in an otherwise healthy organism.

New technology has made possible research studies that could not have been attempted only a few years ago. However, even with these modern research tools, the keys to unlocking the CF puzzle have not yet been found. Nevertheless, physicians continue to refine the contemporary treatment for CF to ensure the best possible quality and length of life for individuals with the disease. These efforts to improve clinical management will continue until basic research provides the critical insights necessary for identifying the fundamental defect(s) in CF and ultimately preventing the disease.

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